SUPPLEMENT

Role of Functional Fortified Dairy Products in Cardiometabolic Health: A Systematic Review and Meta-analyses of Randomized Clinical Trials

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ABSTRACT

There is insufficient evidence on the role of functional fortified dairy products in improving health and in preventing risk factors associated with noncommunicable chronic diseases. This systematic review was conducted to summarize effects of the consumption of fortified dairy products on biomarkers of cardiometabolic risk. MEDLINE and SCOPUS databases were used to perform searches to include studies published up to 30 April 2018. Randomized clinical trials with human subjects consuming dairy products fortified with phytosterols, FAs, vitamins or minerals and relating this consumption with cardiometabolic health were included in this review. Risk of bias assessment according to Cochrane guidelines was performed to determine the quality of the trials. Forty-one studies were finally selected for this synthesis; the selected studies tested dairy products fortified with the following nutrients and bioactive components: phytosterols ($n = 31$), FAs ($n = 8$), and vitamin D ($n = 2$). We found that the consumption of phytosterol-fortified dairy, led to an overall LDL cholesterol reduction of −0.36 (−0.41, −0.31) mmol/L, $P < 0.001$; this decrease was mainly related to the dosage. Likewise, consumption of ω-3 FA-fortified dairy products resulted in a plasma LDL cholesterol reduction of −0.18 (−0.27, −0.09) mmol/L as well as a decrease of −0.18 (−0.32, −0.05) mmol/L in triacylglycerols (TG). Performing meta-analyses of the consumption of dairy products fortified with vitamin D or FAs other than ω-3 FAs and biomarkers of cardiometabolic risk was not possible because of the few available publications. Our results indicate that consumption of dairy products fortified with phytosterols and ω-3 FAs can lead to a reduction of LDL cholesterol and consumption of fortified dairy products fortified with ω-3 FAs can reduce TG concentration. However, more studies with homogeneous designs are needed to determine the advantages of using dairy products as fortification vehicles to prevent cardiometabolic risk. *Adv Nutr* 2019;10:S251–S271.

Keywords: milk, dairy products, fortified food, functional food, biomarker, cardiometabolic health, cardiovascular disease prevention

Introduction

The diet plays an important role in development of healthy habits and is referred to as a modifiable risk factor for a number of noncommunicable chronic diseases (NCCDs) (1–4). According to the WHO, cardiovascular diseases (CVDs) are the main cause of NCCDs deaths (17.9 million people annually) (5, 6). Increased blood pressure, and altered lipid profile (specifically high concentration of LDL cholesterol) (7, 8), as well as inflammatory molecules, for example C-reactive protein and vessel cell adhesion molecules, are well-known risk factors of CVDs (9, 10). In addition, adult populations are at risk of nutrient deficiencies in co-existence with the burden of chronic diseases (11–14).

It has been suggested that improving the nutritional quality of foods is a cost-effective strategy for prevention and management of diseases and this has become a critical issue for policymakers (15, 16). National and international organizations in charge of producing dietary guidelines recommend consumption of ∼ 2–4 servings of dairy/d (6, 17). Indeed, Drouin-Chartier et al. published 2 reviews in 2016 (18, 19) reporting that the consumption of dairy products shows either favorable or neutral association with cardiovascular-related clinical outcomes. In addition, the evidence suggests that the potentially harmful effect of SFAs present in dairy products is balanced by the dairy matrices, concluding that there is no apparent

risk of adverse effects on cardiometabolic risk biomarkers (18, 19).

Fortification is known as the addition of nutrients to foods to improve their quality, and it was initially used to tackle population nutrient deficiencies (20). Fortified dairy products are commonly supplemented with nutrients and other bioactive food components in quantities that are greater than those present normally or that are not present naturally in the food; these products also include the addition of nutrients to compensate for those removed by food processing (20). The latter process is also recognized as enrichment.

Some studies suggest that because of their characteristics, dairy products may represent an excellent vehicle for fortification to deliver critical nutrients, as well as bioactive compounds to improve health biomarkers, some of those biomarkers in people affected by NCCDs (21–24); for example, dairy products fortified with phytosterols (free and esterified sterols and stanols) have been reported to decrease total cholesterol (TC) and LDL cholesterol in hyperlipidemic subjects (25–32), and dairy products fortified with ω-3 FAs to improve cardiovascular risk factors in adults (33–35).

The aim of the present review was to evaluate the potential role of fortified dairy products with bioactive compounds that might have an effect on cardiometabolic health. In that sense, we reviewed the published randomized controlled trials (RCTs) with outcomes related to cardiovascular risk factors regardless of the added compounds.

Methods

The protocol of the present systematic review of randomized, parallel, or crossover clinical trials was registered in the PROSPERO International Prospective Register of Systematic Reviews with the number CRD42018095688, and was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines (36). Furthermore, **Supplemental Table 1** includes the Population, Intervention, Comparison, and Outcomes criteria that were used to answer the following question: *Does the intake of fortified dairy products have any effect on biomarkers of cardiometabolic risk among subjects of all ages, healthy, at risk of disease or nutritional deficiencies, with any acute or chronic diseases?*

Search strategy and eligibility criteria

The literature search was performed by 4 members of the authors' team from 15 March to 30 April 2018, in MEDLINE (via PubMed) and SCOPUS databases, with no limitation related to the publication date. The process of the selection of relevant articles to be included in this systematic review is explained in **Figure 1**. The literature search was complemented by screening references included in previous systematic reviews and meta-analyses.

Our first approach was to find all RCTs testing the functional fortified dairy products and the search was focused on abiotic components (protein, FAs, fiber, vitamins, minerals, and phytosterols); the medical subject headings (MeSH) terms used for our searches were: "functional foods," "food, fortified," "food, formulated," "dairy products," "dietary fiber," "oligosaccharides," "fatty acids, omega-3," "phytosterols," "minerals," and "vitamins." Finally, we selected those articles with outcomes related to cardiometabolic risk factors, regardless of the added bioactive compounds.

Studies in which subjects were exposed to fortified milk or dairy products compared to controls (non-exposed), placebos (unfortified products or products with a regular content of the nutrient of interest), or another treatment group (different levels of exposure or another vehicle of fortification), and specifically testing the role fortified dairy products on biomarkers of cardiometabolic health, were of interest for this systematic review.

Inclusion and exclusion criteria.

We included RCTs, published in English or Spanish, and conducted in humans of all ages and stages of life. Studies developed in healthy subjects; subjects at risk of disease or nutritional deficiencies; subjects in different physiological stages (e.g. pregnancy, menopause, etc.); and subjects with any acute or chronic disease were included in this review. As we focused on studies performed with abiotic components, we excluded all trials that referred to probiotics. No exclusion criterion according to date of publication, sex, gender, race, or location was established.

Data extraction and quality assessment

Articles were organized by bioactive compound used for fortification or enrichment; after that, 3 members of the team extracted information about the characteristics of the subjects participating in each selected study (mean age, BMI, and physiological status), dairy product used as vehicle of fortification, delivered dosage of each compound, and the outcomes related to changes in biomarkers of cardiometabolic risk, for example, TC, LDL cholesterol, TG, and blood pressure.

The quality assessment was performed by 2 authors who independently worked according to the main criteria of the Cochrane Handbook for Systematic Reviews of Interventions (random sequence generation, allocation concealment,

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Address correspondence to MJS-M (e-mail: msoto@finut.org).
Abbreviations used: CVD, cardiovascular disease; NCCD, noncommunicable chronic diseases; RCTs, randomized clinical trials; TC, total cholesterol.

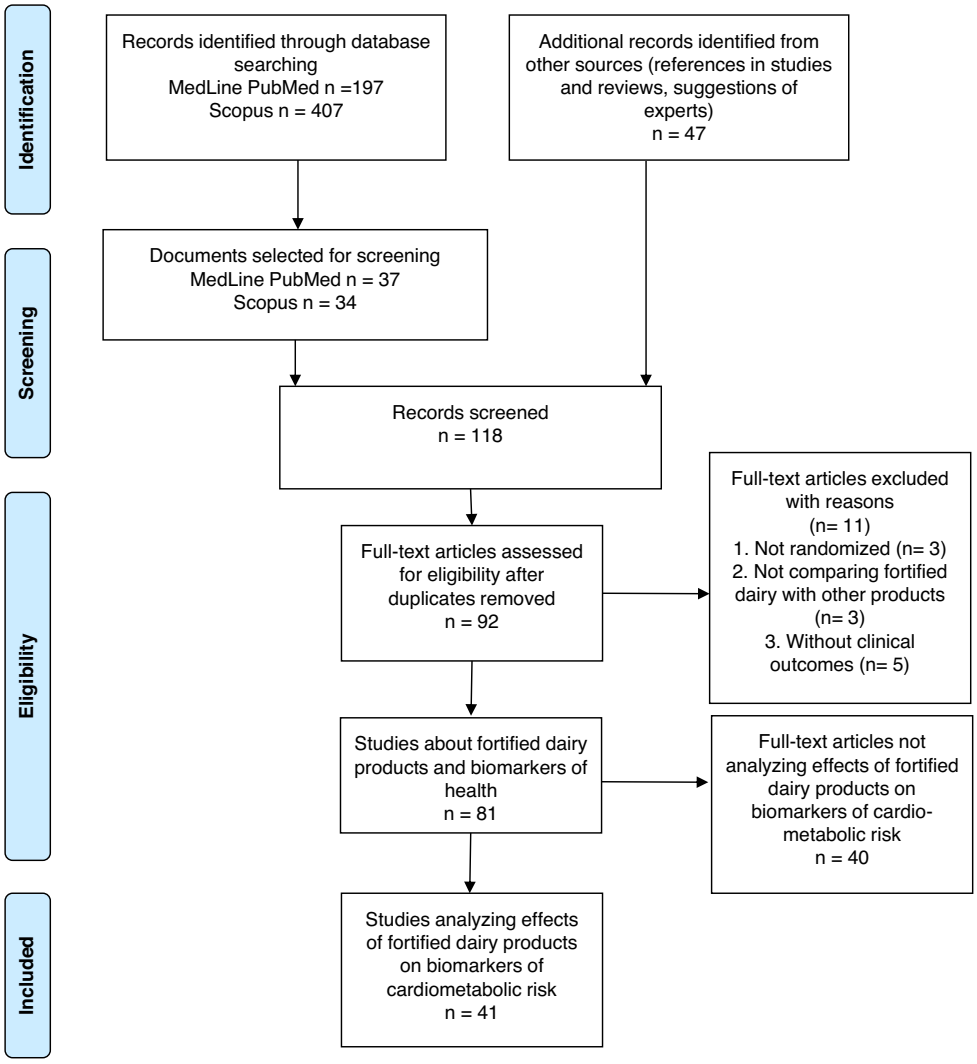

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart for study selection.

blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias) (37); in case of discrepancies, a set of 3 reviewers was involved in the evaluation. The risk of bias was tabulated for each study and classified as low, high, or unclear, following the specific of the Cochrane criteria.

Data handling and analyses

This publication provides a systematic review and meta-analyses of the main findings regarding the effects of fortified dairy products on cardiometabolic risk biomarkers. Meta-analyses were performed with studies that used the same fortification compound (phytosterols and ω-3 FAs) and measured the same cardiometabolic risk biomarker (LDL cholesterol and TG). To evaluate the potential effects of phytosterols added to milk and dairy products, we performed 5 meta-analyses (1 global, which included all dairy; 1 for milk; 1 for yogurt, yogurt drinks, and other fermented milks; 1 for cheese; and 1 for butter). Similarly, we evaluated the effects of ω-3 FA-fortified dairy products using 2 meta-analyses (1 for LDL cholesterol and 1 for TG).

The main outcome variable for the phytosterol meta-analyses was the absolute change in LDL cholesterol concentrations (mmol/L) from baseline to the end of the intervention; whereas, for the ω-3 FAs meta-analyses the main outcomes were changes in LDL cholesterol and TG concentrations (mmol/L) at the end of the intervention period compared with the control groups. The within-trial variance measures for the absolute changes in LDL cholesterol and TG were reported as 95% CI. When the absolute changes in LDL cholesterol and TG were not reported, they were calculated using appropriate formulas (38).

Pooled effect sizes were calculated for the absolute changes in LDL cholesterol and TG following either phytosterol or ω-3 FA intervention using a random-effects model, which takes into account within- and between-study variation. The

estimated results were displayed as forest plots. Between-study heterogeneity was quantified using the I^2 (total heterogeneity divided by total variability). As the presence of heterogeneity may affect the statistical validity of the summary estimate of effect, the Q statistic was used to test the null hypothesis of statistical validity. As RCTs provide general data about subjects, we used a mixed-effects model to evaluate the influences of phytosterol doses, BMI, sex, and age on overall I^2. In addition, we ran tests for age and sex with no significant results (data not shown). Certainty of evidence assessments were performed on our meta-analyses with use of the GRADE Pro GDT application.

Sensitivity analyses were conducted to assess whether any single study elicited undue influence on the overall results. This was conducted by excluding 1 study at a time from the analyses and recalculating the effect size each time. Publication bias was visually assessed using a funnel plot (38).

Statistical analysis was conducted using the R free software environment for statistical computing and graphics, version 3.4.4, R Foundation for Statistical Computing, Vienna. The "metafor" Meta-Analysis Package for R was used for calculations and data visualizations. All data are reported as the mean (95% CI); P values < 0.05 were considered to be significant.

Results

Selection of the randomized clinical trials

We obtained a total of 604 studies after the first search, of which 71 met the inclusion criteria, plus 47 from other sources such as references cited by systematic reviews or papers from the original search that were carefully reviewed by the authors. After screening, we removed 26 duplicates and assessed 92 articles for eligibility. Eighty-one studies were selected for the first approach of collecting RCTs testing fortified dairy products. Forty-one studies were finally selected for this synthesis as they met the criteria of testing fortified dairy products on biomarkers of cardiometabolic risk. This process is further explained in Figure 1, which is based on the PRISMA flow chart. The selected studies tested dairy products fortified with the following nutrients and bioactive compounds: phytosterols (n = 31) (26, 39–68), FAs (n = 8) (69–76), and vitamin D (n = 2) (77, 78), and their effects on a number biomarkers of cardiometabolic risk.

Dairy products fortified with phytosterols and their effect on biomarkers of cardiometabolic risk

We identified 31 RCTs (26, 39–68) quantifying the association between dairy products fortified with phytosterols and plasma lipids related to risk of CVD, particularly TC and LDL cholesterol, and meeting the inclusion criteria. **Table 1** presents descriptive information for the included studies.

The identified RCTs were published between 1995 and 2014: most of them were double-blinded, where both study participants and investigators were unaware of group assignment; 20 had a parallel design and were randomized to 1 of 2 or more intervention groups, and 12 used a crossover design in which participants served as their own control by receiving each intervention, 1 after the other in a random order. Phytosterols were added to dairy products as free sterols or stanols, or as mixtures of sterols and stanol esters and provided an intake in the range of 0.7-4 g/d, expressed as free sterols. The durations of the intervention studies were 3-12 wk. A few included normocholesterolemic subjects, but the majority involved a relatively small number of moderate or hypercholesterolemic subjects. The mean age ranged from 22.3 to 65.0 y, and the mean BMI at baseline ranged from 22.3 to 34.0 kg/m^2 (Table 1).

Eight studies reported data for the association between milk and plasma lipids (39–46); 20 reported data for yogurt, yogurt drinks, and other fermented milks (42, 45, 47-64); 2 reported data for cheese (53, 66) and 4 reported data for butter (26, 65, 67, 68).

The absolute net change in TC reported in the studies ranged from −0.15 mmol/L (95% CI: −0.46, 0.16) to −1.01 mmol/L (95% CI: −1.11, −0.91), and the net change in LDL cholesterol ranged from −0.10 mmol/L (95% CI: −0.037, 0.09) to −0.88 mmol/L (95% CI: −0.99, −0.78).

Figures 2–5 depict the results for the meta-analyses describing the effects of phytosterol-fortified dairy products on the reduction of LDL cholesterol. The overall LDL cholesterol reduction, which included all studies for milk, yogurt, cheese, and butter, was −0.36 mmol/L (95% CI: −0.41, −0.31; $P < 0.001$) (Figure 2).

Significant decreases in LDL cholesterol were also observed for each of the considered dairy products supplemented with phytosterols: milk −0.37 mmol/L (95% CI: −0.47, −0.26; $P < 0.0001$) (Figure 3); yogurt and related products −0.33 mmol/L (95% CI: −0.40, −0.26; $P < 0.001$) (Figure 4); cheese −0.44 mmol/L (95% CI: −0.57, −0.32; $P < 0.001$); and butter −0.43 mmol/L (95% CI −0.51, −0.35; $P < 0.001$) (Figure 5).

The overall average between-trial heterogeneity (I^2) was high at 75.6% (95% CI: 59.5, 81.6; $P < 0.001$), as well as that for milk at 79.8% (95% CI: 56.4, 91.8; $P < 0.001$) and yogurt and related products at 79.9% (95% CI: 62.4, 87.5; $P < 0.001$). However, heterogeneity was low for cheese at 7.21% (95% CI: 0.00, 96.94; $P = 0.3873$), and butter at 0.00 (95% CI: 0.00, 0.00; $P = 0.997$).

A subgroup analysis was conducted to investigate heterogeneity using known factors that might influence circulating LDL cholesterol, such as phytosterol dosage, BMI, age, and sex. In fact, a dose of >3 g/d led to a greater change in LDL cholesterol (−0.55 mmol/L; 95% CI: −0.81, −0.30). Analyses regarding sex and age did not show significant influence (data not shown).

Within those factors, only phytosterol dosage had a significant effect on overall heterogeneity (P = 0.035) (**Supplemental Figures 1** and **2**). In yogurt and other fermented milks, heterogeneity was significantly affected by both phytosterol doses (P = 0.034) and BMI ($P = 0.010$).

TABLE 1 Characteristics of the 31 randomized clinical trials evaluating the effect of supplementation of milk and dairy products supplemented with phytosterols on plasma total cholesterol (TC) and LDL cholesterol of normo- and hypercholesterolemic subjects[1]

Authors (y) (ref)	Type of study (P or CO)	*n* (sample size)	Characteristics of the subjects: age, y; BMI, kg/m^2	Dosage, g/d, and consumption moment	Period of intervention, wk	TC[2], mmol/L	LDL cholesterol[2], mmol/L
Milk							
Bañuls et al. (2010) (39)	P	40	Age: 50.0	2.0 mixture sterol and stanol esters, added to low-fat milk, NR	12	−0.26 (−0.42, −0.10)	−0.21 (−0.30, −0.11)
	—	C = 20	BMI: 28.3	—	—	—	—
	—	T = 20	Moderate hypercholesterolemics	—	—	—	—
Beer et al. (2001) Branch 1 (40)	P	66	Age: 54.8	0.9 mixture sterols and stanols added to low-fat milk, NR	4	NR	−0.33 (−0.57, 0.08)
	—	C = 33	BMI: 27.5	—	—	—	—
	—	T = 33	Hypercholesterolemics	—	—	—	—
Beer et al. (2001) Branch 2 (40)	P	66	Age: 56.4	1.8 mixture sterols and stanols added to low-fat milk, NR	4	NR	−0.38 (−0.61, −0.14)
	—	C = 33	BMI: 27.3	—	—	—	—
	—	T = 33	Hypercholesterolemics	—	—	—	—
Beer et al. (2001) Branch 3 (40)	P	66	Age: 53.3	3.6 mixture sterols and stanols added to low-fat milk, NR	4	NR	−0.57 (0.82, −0.33)
	—	C = 33	BMI: 27.6	—	—	—	—
	—	T = 33	Hypercholesterolemics	—	—	—	—
Casas-Agustench et al. (2012) Branch 1 (41)	CO	43	Age: 49.0	2.0 mixture sterol and stanol esters, added to skimmed milk, with 2 different main meals	4	−0.57 (−0.78, −0.25)	−0.38 (−0.61, −0.02)
	—	—	BMI: 26.6	—	—	—	—
	—	—	Hypercholesterolemics	—	—	—	—
Casas-Agustench et al. (2012) Branch 2 (41)	CO	43	Age: 49.0	2.0 mixture sterol and stanol esters, added to semi-skimmed vegetable fat milk, with 2 different main meals	4	−0.42 (−0.68, −0.16)	−0.34 (−0.56, −0.11)
	—	—	BMI: 26.6	—	—	—	—
	—	—	Hypercholesterolemics	—	—	—	—
Clifton et al. (2004) Branch 2 (42)	CO	58/40	Age: 54.0	1.6 sterol esters added to regular milk, NR	3	−0.66 (−0.74, −0.45)	−0.72 (−0.85, −0.58)
	—	—	BMI: 26.2	—	—	—	—
	—	—	Moderate hypercholesterolomics	—	—	—	—
Hernández-Mijares et al. (2010) (43)	P	55	Age: 49.6	2.0 of a mixture of sterol and stanol esters, added to low-fat milk, twice/d with meals	12	−0.44 (−0.59, −0.31)	−0.43 (−0.55, −0.31
	—	C = 24	BMI: 27.3	—	—	—	—
	—	T = 31	Hypercholesterolomics	—	—	—	—
Hernández-Mijares et al. (2011) (44)	P	48	Age: 51.5	2.0 of a mixture of sterol and stanol esters, added to low-fat milk, twice/d with meals	12	−0.26 (−0.36, −0.16)	−0.12 (−0.22, −0.02)
	—	C = 24	BMI: 31.1	—	—	—	—
	—	T = 24	Moderate hypercholesterolomics	—	—	—	—

(*Continued*)

TABLE 1 (*Continued*)

Authors (y) (ref)	Type of study (P or CO)	*n* (sample size)	Characteristics of the subjects: age, y; BMI, kg/m^2	Dosage, g/d, and consumption moment	Period of intervention, wk	TC[2], mmol/L	LDL cholesterol[2], mmol/L
Seppo et al. (2007) Study 4 (45)	P	59	Age: 46.7	2.0 stanol esters, added to low-fat milk, NR	5	NR	−0.21 (−0.38, −0.05)
	—	C = 27	BMI: 25.2	—	—	—	—
	—	T = 32	Normocholesterolomics	—	—	—	—
Thomsen et al. (2004) Branch 1 (46)	CO	69	Age: 60	1.2 free sterols, added to low-fat milk, with breakfast and lunch	4	−0.35 (−0.43, −0.26)	−0.34 (−0.52, −0.16)
	—	—	BMI: 25.9	—	—	—	—
	—	—	Hypercholesterolomics	—	—	—	—
Thomsen et al. (2004) Branch 2 (46)	CO	69	Age: 60	1.6 free sterols, added to low-fat milk, with breakfast and lunch	4	−0.49 (−0.54, 0.44)	−0.44 (−0.64, −0.24)
	—	—	BMI: 25.9	—	—	—	—
	—	—	Hypercholesterolomics	—	—	—	—
Yogurt, yogurt drinks and other fermented milks							
Algorta-Pineda et al. (2005) (47)	P	32	Age: 42	2.0 stanol esters, added to yogurt drink, with the main meal	3	NR	−0.34 (−0.66, −0.01)
	—	C = 15	BMI: 26.0	—	—	—	—
	—	T = 17	Moderate hypercholesterolomics	—	—	—	—
Buyuktuncer et al. (2013) (48)	P	70	Age: 45.5	1.9 stanol esters, added to low-fat yogurt, with lunch	4	−0.45 (−0.66, −0.24)	−0.26 (−0.41, −0.11)
	—	—	BMI: 27.9	—	—	—	—
	—	—	Hypercholesterolomics	—	—	—	—
Clifton et al. (2004) Branch 4 (42)	CO	58/40	Age: 54.0	1.6 sterol esters added to yogurt, NR	3	−0.26 (−0.54, −0.19)	−0.36 (−0.50, −0.22)
	—	—	BMI: 26.2	—	—	—	—
	—	—	Moderate hypercholesterolomics	—	—	—	—
Doornbos et al. (2006) (49)	P	71	Age: 56.8	2.8 to 3.2 sterol esters added to low-fat yogurt drink, with breakfast or lunch	4	NR	−0.37 (−0.49, −0.25)
	—	C = 33	BMI: 25.2	—	—	—	—
	—	T = 38	Moderate hypercholesterolomics	—	—	—	—
Hansel et al. (2007) (50)	P	204	Age: 56.8	1.6 sterol esters added to low-fat fermented milk, NR	6	NR	−0.32 (−0.45, −0.19)
	—	C = 99	BMI: 25.2	—	—	—	—
	—	T = 95	Moderate hypercholesterolomics	—	—	—	—
Hyun et al. (2005) (51)	P	51	Age: 28.7	2.8 stanol esters added to yogurt with breakfast	4	−0.15 (−0.46, 0.16)	−0.24 (−0.43, −0.06)
	—	C = 28	BMI: 22.6	—	—	—	—
	—	T = 23	Normocholesterolemics	—	—	—	—
Khandelwal et al. (2009) (52)	P	93	Age: 46.0	2.0 sterol esters added to a yogurt drink, with lunch	4	−020 (−0.36, −0.04)	−0.17 (−0.33, −0.01)
	—	—	BMI: 24.8	—	—	—	—
	—	—	Moderate hypercholesterolemics	—	—	—	—

(*Continued*)

TABLE 1 (*Continued*)

Authors (y) (ref)	Type of study (P or CO)	*n* (sample size)	Characteristics of the subjects: age, y; BMI, kg/m^2	Dosage, g/d, and consumption moment	Period of intervention, wk	TC[2], mmol/L	LDL cholesterol[2], mmol/L
Korpela et al. (2006) Study 1 (53)	P	50	Age: 57.3	1.65 of a mixture of free sterols and stanols added to yogurt, NR	6	NR	−0.32 (−0.58, −0.06)
	—	C = 25	BMI: 27	—	—	—	—
	—	T = 25	Moderate hypercholesterolemics	—	—	—	—
Mannarino et al. (2009) (54)	P	116	Age: 50.1	1.6 sterol esters added to a fermented milk, with lunch or dinner	3	−0.83 (−0.86, −0.80)	−0.49 (−0.53, −0.41)
	—	—	BMI: 25	—	—	—	—
	—	—	Hypercholesterolemics	—	—	—	—
Mensink et al. (2002) (55)	P	60	Age: 36.0	3.0 stanol esters added to yogurt, with each meal or breakfast and supper	4	NR	−0.40 (−0.53, −0.26)
	—	C = 30	BMI: 23.3	—	—	—	—
	—	T = 30	Normocholesterolemics	—	—	—	—
Niittynen et al. (2008) Study 1 (56)	CO	15	Age: 41.0	1.0 free sterols added to low-fat yogurt drink, NR	4	NR	−0.19 (−0.41, 0.03)
	—	—	BMI: 25.6	—	—	—	—
	—	—	Normocholesterolemics	—	—	—	—
Niittynen et al. (2008) Study 2 (56)	P	26	Age: 47.1	2.0 free sterols added to low-fat yogurt drink, NR	8	NR	−0.28 (−0.88, 0.29)
	—	C = 14	BMI: 25.6	—	—	—	—
	—	T = 12	Hypercholesterolemics	—	—	—	—
Noakes et al. (2005) study 2, branch 1 (57)	CO	40	Age: 60.4	1.8 sterol esters added to yogurt, NR	3	NR	−0.23 (−0.33, −0.13)
	—	—	BMI: 26.5	—	—	—	—
	—	—	Hypercholesterolomics	—	—	—	—
Noakes et al. (2005) study 2, branch 2 (57)	CO	40	Age: 60.4	1.7 stanol esters added to yogurt; NR	3	NR	−0.27 (−0.37, −0.17)
	—	—	BMI: 26.5	—	—	—	—
	—	—	Hypercholesterolomics	—	—	—	—
Plana et al. (2008) (58)	P	83	Age: 51.3	1.6 as free sterol esters, added to yogurt, with lunch	6	−0.50 (−1.12, −0.26)	−0.43 (−0.72, −0.16)
	—	C = 40	BMI: 26.7	—	—	—	—
	—	T = 43	Hypercholesterolomics	—	—	—	—
Plat et al. (2009) (59)	P	36	Age: 51.3	2.0 stanol esters added to a yogurt drink, with each meal	9	−0.75 (−1.22, −0.32)	−0.43 (−1.15, −0.22)
	—	C = 19	BMI: 26.7	—	—	—	—
	—	T = 17	Metabolic syndrome treated with statins	—	—	—	—
Rudkowska et al. (2008) (60)	CO	26	Age: 59.6	1.6 free sterols, added to a low-fat yogurt, with a meal or over an afternoon snack	4	0.45 (−0.65, −0.25)	−0.23 (−0.43, −0.03)
	—	—	BMI: 26.4	—	—	—	—
	—	—	Hypercholesterolomics	—	—	—	—

(*Continued*)

TABLE 1 (*Continued*)

Authors (y) (ref)	Type of study (P or CO)	*n* (sample size)	Characteristics of the subjects: age, y; BMI, kg/m^2	Dosage, g/d, and consumption moment	Period of intervention, wk	TC[2], mmol/L	LDL cholesterol[2], mmol/L
Ruiu et al. (2009) (61)	P	15	Age: 54.2	1.0 sterol esters added to a yogurt drink, with breakfast	4	−0.21 (−0.35, −0.07)	−0.31 (−0.43, −0.19)
	—	—	BMI: 24.3	—	—	—	—
	—	—	Hypercholesterolomics	—	—	—	—
Seppo et al. (2007) Study 1 (45)	P	60	Age: 46.7	2.0 stanol esters added to yogurt, NR	5	NR	−0.10 (−0.31, 0.12)
	—	C = 29	BMI: 25.2	—	—	—	—
	—	T = 31	Normocholesterolomics	—	—	—	—
Seppo et al. (2007) Study 2 (45)	P	61	Age: 46.7	2.0 stanol esters added to low-fat yogurt drink, NR	5	NR	−0.11 (−0.31, 0.09)
	—	C = 32	BMI: 25.2	—	—	—	—
	—	T = 29	Normocholesterolomics	—	—	—	—
Seppo et al. (2007) Study 3 (45)	P	19	Age: 46.7	2.0 stanol esters added to low-fat yogurt drink, with lunch	5	NR	−0.40 (−0.84, 0.03)
	—	C = 9	BMI: 25.2	—	—	—	—
	—	T = 10	Normocholesterolomics	—	—	—	—
Sialvera et al. (2012) (62)	P	108	Age: 30–65	4.0 mixture of sterols and stanols, added to a yogurt drink, with lunch and dinner	8	−1.01 (−1.11, −0.91)	−0.88 (−0.99, −0.78)
	—	C = 55	BMI: 28–34	—	—	—	—
	—	T = 53	Hypercholesterolemics	—	—	—	—
Vasquez-Trespalacios et al. (2014) (63)	CO	40	Age: 37.9	4.0 stanol esters added to yogurt, 2 portions as part of main meals	4	−0.41 (−0.70, −0.12)	−0.32 (−0.56, −0.07
	—	—	BMI: 25.0	—	—	—	—
	—	—	Hypercholesterolemics	—	—	—	—
Volpe et al. (2001) (64)	CO	30	Age: -	1.1 free sterols added to low-fat yogurt drink, NR	4	NR	−0.34 (−0.51, −0.17)
	—	—	BMI: 24.4	—	—	—	—
	—	—	Hypercholesterolemics	—	—	—	—
Cheese							
Jauhiainen et al. (2006) (66)	P	67	Age: 43.3	2.0 g/d of stanol esters added to hard cheese, with each meal or at lunch	5	−0.32 (−0.50, −0.15)	−0.36 (−0.53, −0.18)
	—	C = 34	BMI: -Normocholesterolemics	—	—	—	—
	—	T = 33	—	—	—	—	—
Korpela et al. (2006) Study 1 (53)	P	62	Age: 57.3	2.0 of a mixture of free sterols and stanols added to hard cheese, NR	6	NR	−0.46 (−0.71, −0.21)
	—	C = 29	BMI: 27.0	—	—	—	—
	—	T = 33	Moderate hypercholesterolemics	—	—	—	—

(*Continued*)

TABLE 1 (*Continued*)

Authors (y) (ref)	Type of study (P or CO)	*n* (sample size)	Characteristics of the subjects: age, y; BMI, kg/m^2	Dosage, g/d, and consumption moment	Period of intervention, wk	TC[2], mmol/L	LDL cholesterol[2], mmol/L
Korpela et al. (2006) Study 2 (53)	P	62	Age: 57.3	2.0 of a mixture of free sterols and stanols added to fresh cheese, NR	6	NR	−0.56 (−0.8, −0.32)
	—	C = 28	BMI: 27.0	—	—	—	—
	—	T = 24	Moderate hypercholesterolemics	—	—	—	—
Butter							
Charest et al. (2004) (67)	CO	14	Age: 48.6	1.8 phytosterols added to butter, with each meal	3	−0.60 (−1.29, −0.09)	−0.50 (−1.05, 0.05)
	—	—	BMI: 30.9	—	—	—	—
	—	—	Moderate hypercholesterolemics	—	—	—	—
Gylling and Miettinen (1999) (26)	CO	21	Age: 52.7	2.4 stanol esters added to butter, NR	5	NR	−0.45 (−0.66, −0.24)
	—	—	BMI: 25.7	—	—	—	—
	—	—	Moderate hypercholesterolemics	—	—	—	—
Pelletier et al. (1995) (68)	CO	12	Age: 22.7	0.74 free sterols added to butter, NR	4	−0.44 (−0.60, −0.28)	−0.41 (−0.55, −0.27)
	—	—	BMI: 22.3	—	—	—	—
Vanstone et al. (2002) Branch 1 (65)	CO	15	Age: 47.8	1.8 free sterols added to butter, with each meal	3	NR	−0.41 (−0.65, −0.17)
	—	—	BMI: 30.8	—	—	—	—
	—	—	Moderate hypercholesterolemics	—	—	—	—
Vanstone et al. (2002) Branch 2 (65)	CO	15	Age: 47.8	1.8 free stanols added to butter, with each meal	3	NR	−0.42 (−0.66, −0.18)
	—	—	BMI: 30.8	—	—	—	—
	—	—	Hypercholesterolemics	—	—	—	—
Vanstone et al. (2002) Branch 3 (65)	CO	15	Age: 47.8	1.8 mixture free sterols and stanols, added to butter, with each meal	3	NR	−0.46 (−0.70, −0.22)
	—	—	BMI: 30.8	—	—	—	—
	—	—	Hypercholesterolemics	—	—	—	—

[1] CO, crossover; NR, pattern of consumption not reported; P, parallel; ref, reference; TC, total cholesterol; y, year.
[2] Differences between treated and control groups, expressed as mean difference and 95% CI.

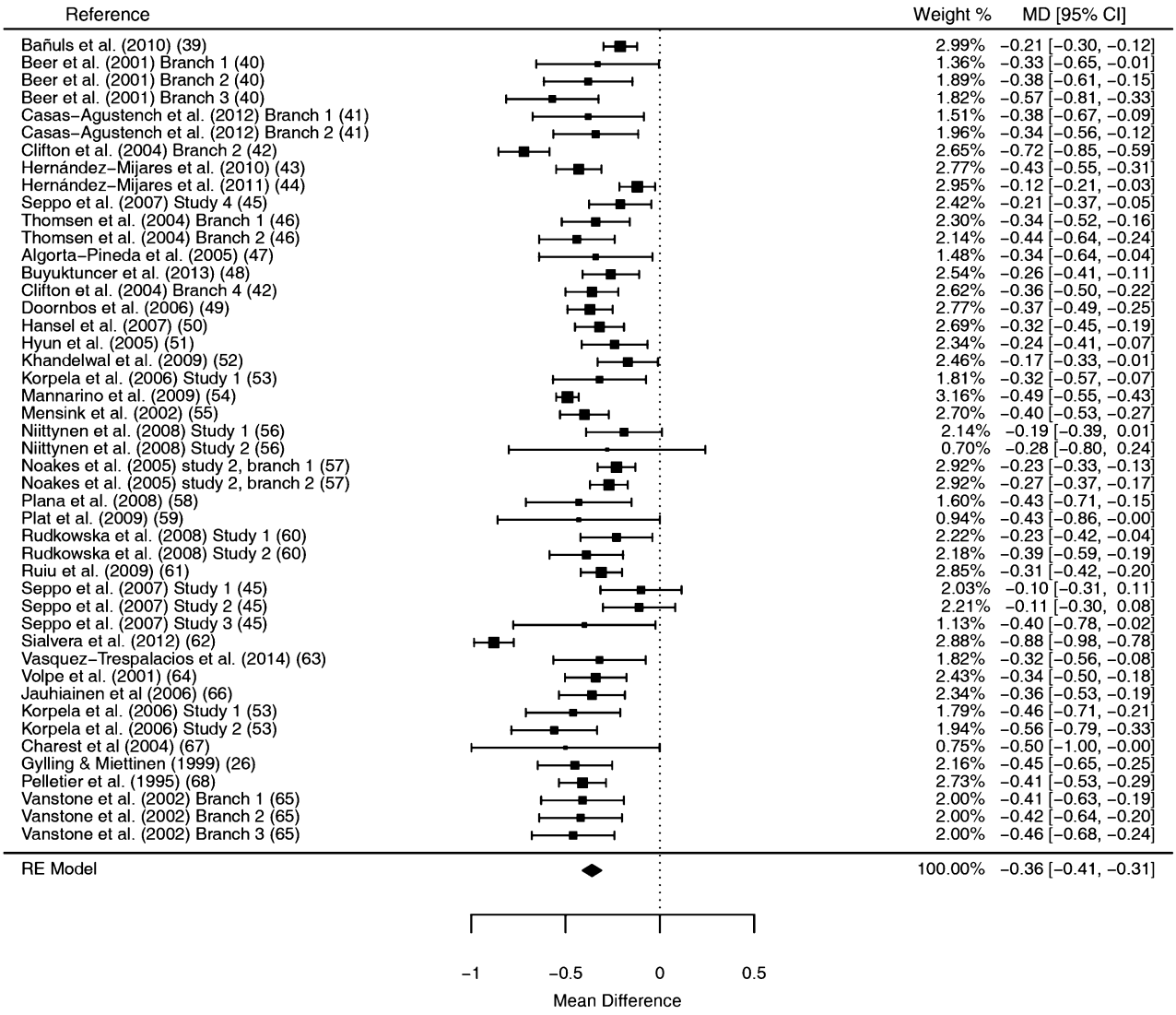

FIGURE 2 Effect size and 95% CI for fully adjusted random-effects model evaluating the influence of consumption of dairy products fortified with phytosterols on LDL cholesterol plasma concentrations. Overall effect: Z = − 14.33, $P < 0.001$; Heterogeneity: $I^2 = 75.6\%$ (59.12, 81.60), Q = 226.99, df = 45, $P < 0.001$ ($n = 46$). Pooled effect estimate is represented by the black diamond. MD, mean difference; RE model, random effect model.

Dairy products fortified with FAs and their effect on biomarkers of cardiometabolic risk

Eight studies, published between 2009 and 2016, that included interventions with dairy products fortified with bioactive lipids in healthy subjects are presented in **Table 2**.

One article was based on supplementation of healthy children. Romeo et al. (69) studied the effects of consuming 600 mL/d of an enriched dairy product containing EPA (60 mg) and DHA (120 mg), among other nutrients, for 5 mo. The outcomes measured included the impact on lipid profile, and other cardiometabolic risk biomarkers. The authors reported a mean difference of −0.12 mmol/L (95% CI: −0.32, 0.08 mmol/L) for LDL cholesterol and of −0.04 mmol/L (95% CI −0.17, 0.09) for TG; in addition they reported a significant decrease in the indexes of endothelial cell activation, such as a decrease of E-selectin only in the supplemented group ($P < 0.05$), whereas VCAM-1 also decreased in the supplemented group but only in the boys (P-interaction treatment × sex = 0.038).

Moreover, 2 studies reported the effect of bioactive lipids on healthy adults. Firstly, Ohlsson et al. (70) reported that milk-like formulation, containing 975 mg of milk sphingomyelins, might affect the cholesterol concentrations in TG-rich lipoproteins without affecting the postprandial TGs. Secondly, the inclusion of dairy products containing *cis*-9, *trans*-11 CLA did not impact blood pressure or heart rate after 9 wk (71).

Four studies were developed in subjects with metabolic abnormalities; 2 included subjects with mild hypertriglyceridemia [$n = 49$ (72) and $n = 53$ (73)], and 2 studies included

TABLE 2 Characteristics of the 8 studies analyzing the effects of the intake of dairy products fortified with ω-3 FA on plasma TG, LDL cholesterol, and blood pressure, in healthy subjects and adults with moderate risk of cardiovascular disease[1]

Authors (y) (ref)	Type of study (P or CO)	*N* (sample size)	Characteristics of the subjects: age, y; BMI, kg/m^2	Dosage, g/d	Period of intervention	TG[2], mmol/L	LDL cholesterol[2], mmol/L
Dawczynski et al. (2010) (72)	CO	49	Age: 59	Dairy products enriched with 3 g ω-3 LC-PUFA/d, NR	30 wk	-0.28 (-0.68, 0.12)	NC
	—	—	BMI: 29.7	—	—	—	—
	—	—	Mildly hypertriacylglycerolemic subjects (TG $\geq$ 1.5 mmol/L)	—	—	—	—
Dawczynski et al. (2013) Branch 1 (73)	P	31	Age: 60.5	125 g of yoghurt enriched with 0.8 g ω-3 LC-PUFA/d, NR	10 wk	−0.18 (−0.50, 0.14)	−0.13 (−0.39, 0.65)
	—	C = 14	BMI: 26.2	—	—	—	—
	—	T = 17	Mildly hypertriacylglycerolemic subjects (TG 1.7 mmol/L)	—	—	—	—
Dawczynski et al. (2013) Branch 2 (73)	P	31	Age: 60.5	125 g of yoghurt enriched with 3 g ω-3 LC-PUFA/d, NR	10 wk	−0.05 (−0.43, 0.33)	−0.25 (−0.23, 0.73)
	—	C = 14	BMI: 26.2	—	—	—	—
	—	T = 17	Mildly hypertriacylglycerolemic subjects (TG 1.7 mmol/L)	—	—	—	—
Engberink et al. (2012) (71)	CO	61	Age: 30.9	7% of energy (18.9 g in a diet of 10 MJd^{-1}) that was provided either by oleic acid, by industrial *trans* FA or by *cis*-9, *trans*-11 CLA, with lunch	9 wk	NR	NR
	—	—	BMI: 22.8	—	—	—	—
	—	—	Healthy subjects	—	—	—	—
Fonollá et al. (2009) (74)	P	208	Age: 46	500 mL/d of enriched milk (oleic acid, 54.4 mg/100 g of fat; EPA + DHA, 3.5 g/100 g of fat), NR	1 y	−0.35 (−0.39, −0.31)	−0.26 (−0.29, −0.23)
	—	C = 107	BMI: 28.8	—	—	—	—
	—	T = 101	Adults with moderate CVD risk	—	—	—	—
Fonolla-Joya et al. (2016) (75)	P	117	Age: 45	500 mL/d of a low-lactose skimmed milk enriched (with 40 mg/100 mL of EPA + DHA), NR	1 y	−0.17 (−0.21, −0.13)	−0.18 (−0.23, −0.13)
	—	C = 54	BMI: 29.9	—	—	—	—
	—	T = 63	Postmenopausal women with moderate CVD risk	—	—	—	—

(*Continued*)

TABLE 2 (*Continued*)

Authors (y) (ref)	Type of study (P or CO)	*N* (sample size)	Characteristics of the subjects: age, y; BMI, kg/m^2	Dosage, g/d	Period of intervention	TG[2], mmol/L	LDL cholesterol[2], mmol/L
Knapen et al. (2015) (76)	P	56	Age: 57	drinking yogurt with ω-3 FAs (40 mg), Mg (56 mg), Ca (108 mg), vitamin C (12 mg), vitamin D3 (0.75 μg), and vitamin K 56 μg/d, twice/d	12 wk	0.11 (−0.07, 0.029)	−0.09 (−0.41, 0.24)
	—	C = 29	BMI: 25.4	—	—	—	—
	—	T = 27	Healthy men and postmenopausal women	—	—	—	—
Ohlsson et al. (2010) (70)	CO	18	Age: 39	Milk-like formulation (containing 975 mg of milk SL; 700 mg sphingomyelin, 180 mg glucoceramides, and 95 mg gangliosides), with breakfast	1, 3, 5 and 7 h	NR	NR
	—	—	BMI: 24.3	—	—	—	—
	—	—	Healthy male adults	—	—	—	—
Romeo et al. (2011) (69)	P	40	Age: 11.4	600 mL/d of enriched dairy product ω-3 35 mg/100 mL	12 wk	−0.04 (−0.17, −0.09)	−0.12 (−0.32, −0.08)
	—	C = 53	BMI: 19.8	DHA 20 mg/100 mL	—	—	—
	—	T = 54	Healthy children	EPA 10 mg/100 mL, as breakfast and as afternoon snack	—	—	—

[1] CO, crossover; CVD, cardiovascular disease; LC-PUFA, long-chain polyunsaturated fatty acids; NC, no changes; NR, pattern of consumption not reported; P, parallel; ref, reference; SL, sphingolipids; TC, total cholesterol; y, year.
[2] Decrease over time expressed as mean change and 95% CI.

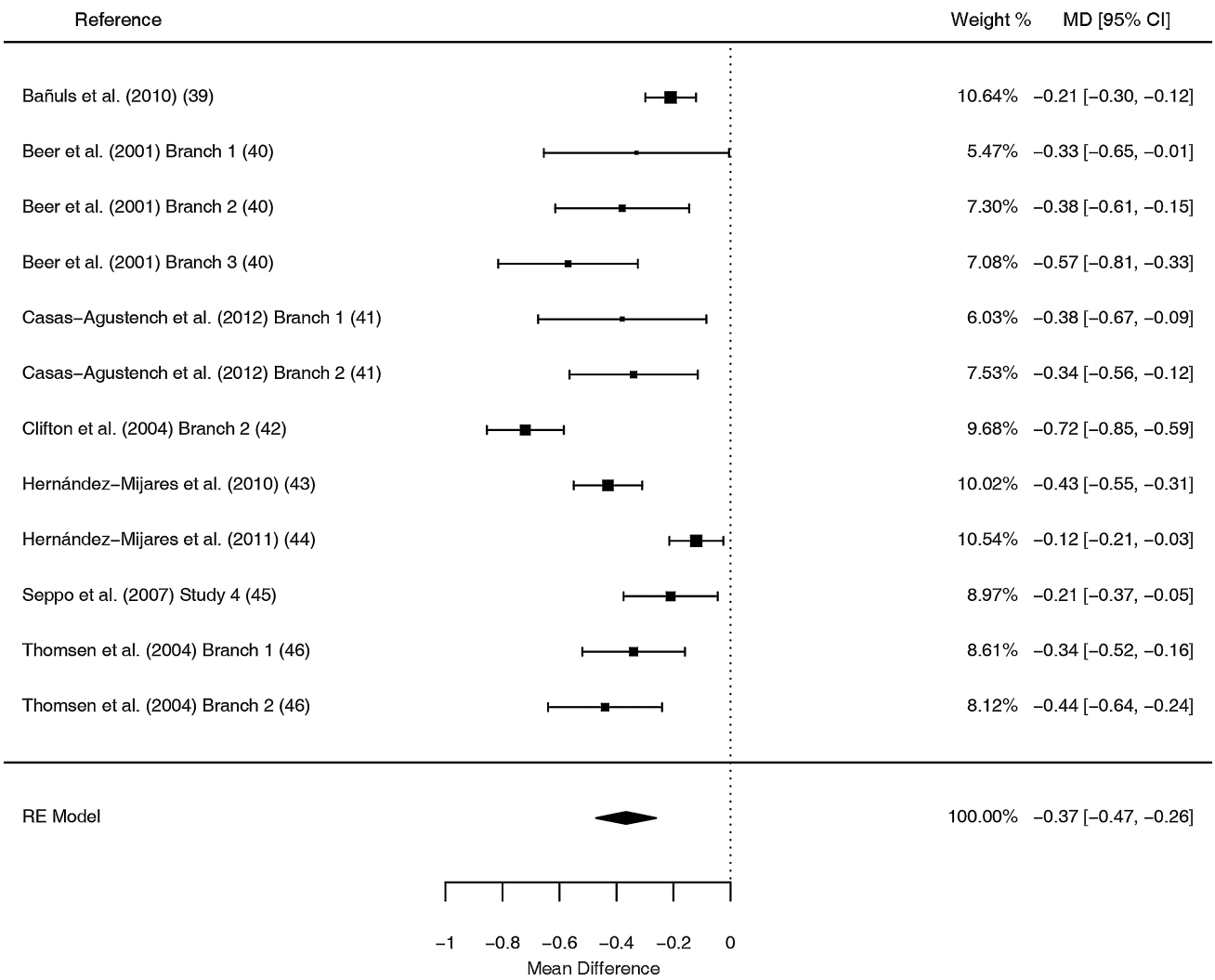

FIGURE 3 Effect size and 95% CI for fully adjusted random-effects model evaluating the influence of consumption of milk fortified with phytosterols on LDL cholesterol plasma concentrations. Overall effect: $Z = -6.84$, $P < 0.001$; Heterogeneity: $I^2 = 79.8\%$ (56.45, 91.71), $Q = 67.52$, df = 11, $P < 0.001$ ($n = 12$). Pooled effect estimate is represented by the black diamond. MD, mean difference; RE model, random effect model.

subjects with a moderate cardiovascular risk [n = 297 (74) and n = 117 (75)]. Dawczynski et al. (72) investigated the effect of including 40 g of fat from dairy products for 15 wk on the prevention of atherosclerosis and congenital heart defect; they reported a reduction of several risk factors for congenital heart defect, such as TC, TG, and the TC/HDL cholesterol and LDL cholesterol/HDL cholesterol ratios. Later, the same authors studied the effect of different doses of ω-3 FAs (0.8 and 3 g/d), using yogurt as a vehicle, for 10 wk (73). The principal outcomes were related to a dose-dependent improvement of several CVD risk factors, such as ω-3 FAs index, HDL cholesterol, TG, and LDL cholesterol/HDL cholesterol arachidonic acid/EPA ratio in plasma and red blood cells. In addition, the 3 g dose of ω-3 FAs decreased several arachidonic acid-derived eicosanoids and increased EPA-derived mediators. Furthermore, the authors detected that the ability of ω-3 FAs to regulate TG and HDL cholesterol was associated with the CD36 genotype.

Fonollá et al. (74, 75) reported that the consumption of 500 mL/d of fortified milk with a mixture of high polyunsaturated vegetable fat (containing 3.5 g of EPA + DHA/100 g fat) by 297 adults with moderate cardiovascular risk for 12 months decreased TC, LDL cholesterol, and TG, and increased HDL cholesterol but had no effect on other CV risk factors (74). Then, a similar intervention including only postmenopausal women resulted in a decrease of TC, LDL cholesterol, LDL cholesterol/HDL cholesterol ratio, high-sensitivity C-reactive protein, and glucose (all $P < 0.05$) (75).

Yogurt-fortified EPA and DHA (36.3 mg or 15% of the daily recommendation) combined with other micronutrients (vitamin K, vitamin D, ascorbic acid, calcium and magnesium), and delivered to mixed groups of adults (men and

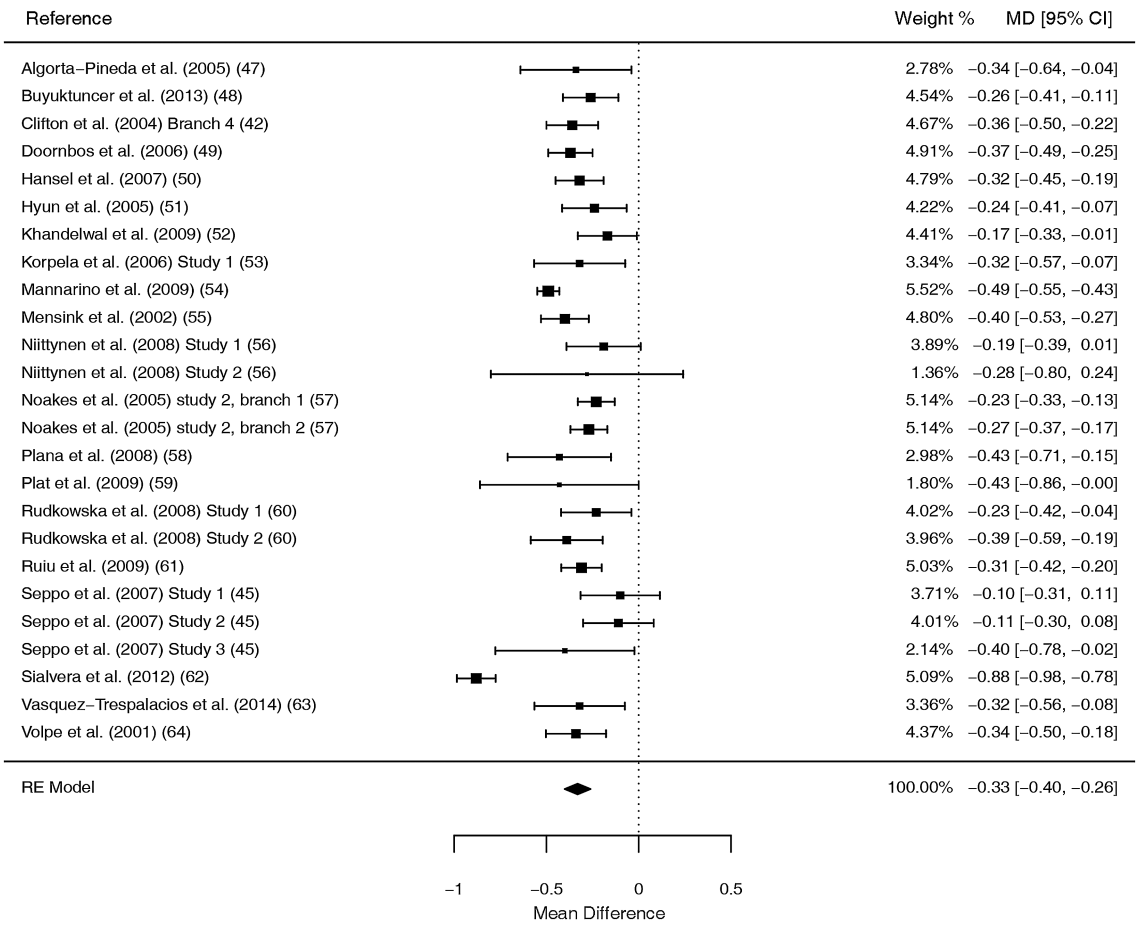

FIGURE 4 Effect size and 95% CI for fully adjusted random-effects model evaluating the influence of consumption of yogurt, yogurt drinks and other fermented milks fortified with phytosterols on LDL cholesterol plasma concentrations. Overall effect: $Z = -9.32$, $P < 0.001$; Heterogeneity: $I^2 = 79.9\%$ (62.38, 87.53), Q = 148.47, df = 24, $P < 0.001$ ($n = 25$). Pooled effect estimate is represented by the black diamond. MD, mean difference; RE model, random effect model.

postmenopausal women) improved vitamin K ($P = 0.004$), D ($P = 0.005$), and C ($P = 0.048$) status. However, the EPA and DHA status were not measured and the fortified yogurt did not change lipid metabolism biomarkers after 6 and 12 wk of intervention (76).

Because of the methodologies used by the RCT authors, we could perform meta-analyses including 4 studies (69, 73, 74, 75) to test the effects of dairy products fortified with ω-3 FAs on 2 biomarkers of cardiometabolic risk: LDL cholesterol and TG. **Figure 6** depicts results of the meta-analysis describing the effects of ω-3 FA-fortified dairy products on the reduction of LDL cholesterol. The overall LDL cholesterol reduction, which included 5 studies, was −0.18 mmol/L (95% CI −0.27, −0.09; $P < 0.001$). The meta-analysis that describes the effects of dairy product fortification with ω-3 FAs on reduction of TG is included in **Figure 7**. The overall TG reduction, including the same 5 studies was −0.18 mmol/L (95% CI −0.32, −0.50; $P = 0.008$) (Figure 7). Between-trial heterogeneity (I^2) was high for LDL cholesterol meta-analyses (77.5%; 95% CI: 19.32, 99.58%; $P < 0.0001$), and very high (91.5%; 95% CI: 66.40, 98.82%) for TG.

Milk and dairy products fortified with vitamin D and their effect on biomarkers of cardiometabolic risk

Two studies reporting fortification of dairy products with vitamin D were found in our search, details of these studies are presented in **Table 3**. Toxqui et al. (77) evaluated the blood pressure and lipid concentrations of 165 young women with low Fe status after 16-wk consumption of skimmed milk fortified with vitamin D and Fe. The authors reported reductions in systolic ($P = 0.017$) and diastolic ($P = 0.010$) blood pressure, but no changes in TC, HDL cholesterol, TG, or glucose. A study carried out by Li and Xing in 2016 (78) measured insulin resistance and lipid profile, after a 16-wk intervention with a vitamin D-fortified yogurt in mothers with gestational diabetes mellitus. The authors reported a decrease in TG (mean ± SD 0.45 ± 0.48 compared with −0.27 ± 0.49 mmol/L; $P = 0.02$), TC (0.55 ± 0.97 compared with −0.60 ± 0.98 mmol/L, $P = 0.04$), LDL cholesterol

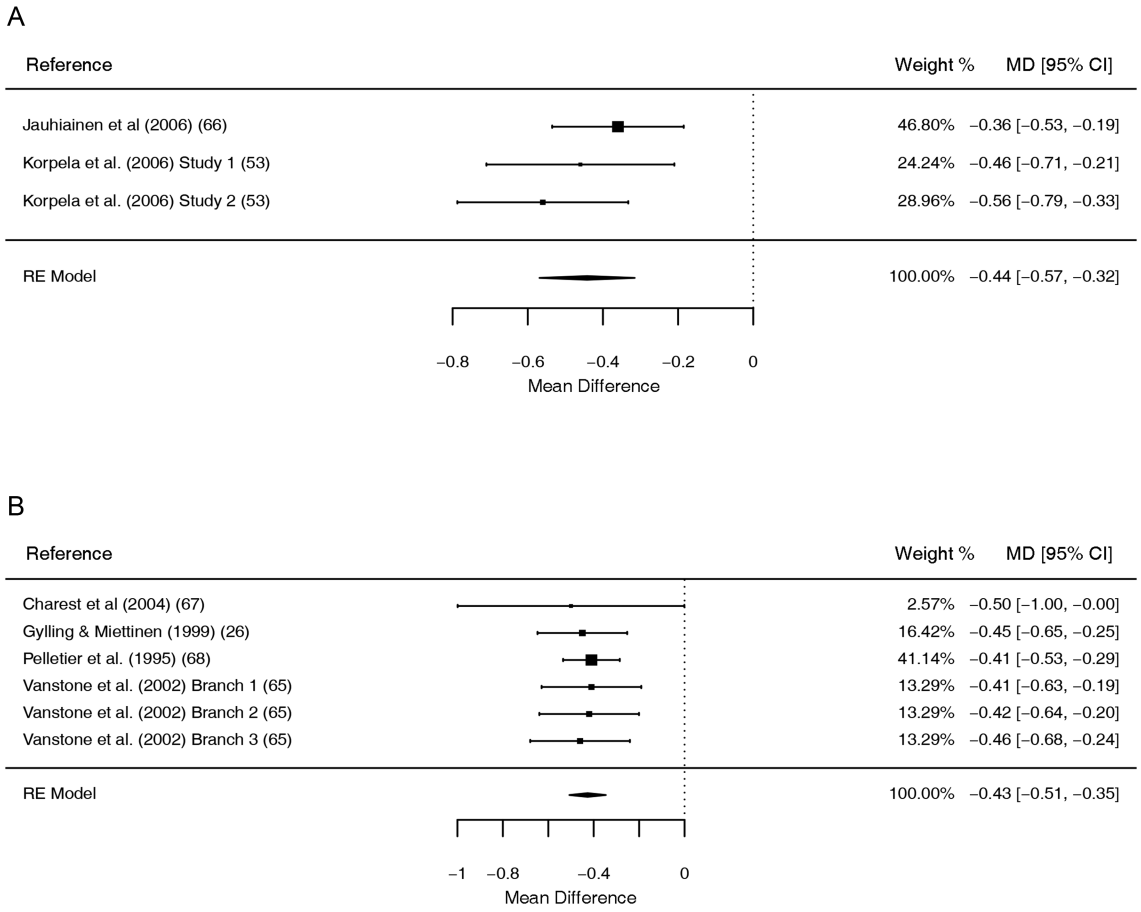

FIGURE 5 Effect size and 95% CI for fully adjusted random-effects model evaluating the influence of consumption of cheese [overall effect: Z = − 6.85, $P < 0.001$; Heterogeneity: $I^2 = 7.2\%$ (0.0001, 96.95), Q = 1.90, df = 2, $P = 0.39$ ($n = 3$)] (A) and butter [overall effect: Z − 10.46, $P < 0.001$; Heterogeneity: $I^2 = 0.0\%$ (0, 0), Q = 0.32, df = 5, $P = 1.00$ ($n = 6$)] (B) fortified with phytosterols on LDL cholesterol plasma concentrations. Pooled effect estimate is represented by the black diamond. MD, mean difference; RE model, random effect model.

(0.21 ± 0.58 compared with −15.3 ± 21.7 mmol/L; $P = 0.05$), and the ratio of TC/HDL cholesterol (0.4 ± 0.6 compared with −0.3 ± 0.3; $P = 0.02$).

Risk of bias, and certainty of evidence

The risk of bias summaries and graphs, based on the Cochrane Collaboration guidelines, are included as supplemental material. **Supplemental Figure 3** shows the summary and graph of the risk of bias assessment for the articles on fortification of dairy products with phytosterols (n = 30); we did not evaluate the study by Beer et al. (40), because it is not a published article and the results are only available in a series of reviews and US FDA documents. The majority of the studies have an unclear risk of bias for allocation concealment because the authors did not explain the methods properly, even when the title explained that the study was a randomized controlled trial. One study was categorized as having a high risk of bias for random sequence generation and allocation concealment. No reporting bias was found in this group of RCTs.

The summary and graph of the risk of bias assessment for the articles on dairy fortification with ω-3 FAs (n = 8) are presented in **Supplemental Figure 4.** The majority of studies (6 of 8) were categorized as unclear selection bias; the risks for performance, attrition, and reporting bias, were considered as low. Risk of bias summary and graph for the 2 articles testing dairy fortification with vitamin D ($n = 2$) are included in **Supplemental Figure 5**.

The sensitivity study of bias for phytosterol-fortified milk, yogurt, and other fermented milks, cheese, and butter are depicted in funnel plots (**Supplemental Figures 6-9**). The sensitivity study of bias for ω-3 FA-fortified dairy products is presented in **Supplemental Figure 10**; panel **A** shows changes in LDL cholesterol and panel **B** changes in TG.

Certainty of evidence assessments were performed on our meta-analyses with use of the GRADE Pro GDT application combining risk of bias results based on the Cochrane criteria and meta-analyses results of heterogeneity. **Supplemental Tables 2** and **3** show that the certainty of evidence was *high* for the meta-analyses evaluating butter and

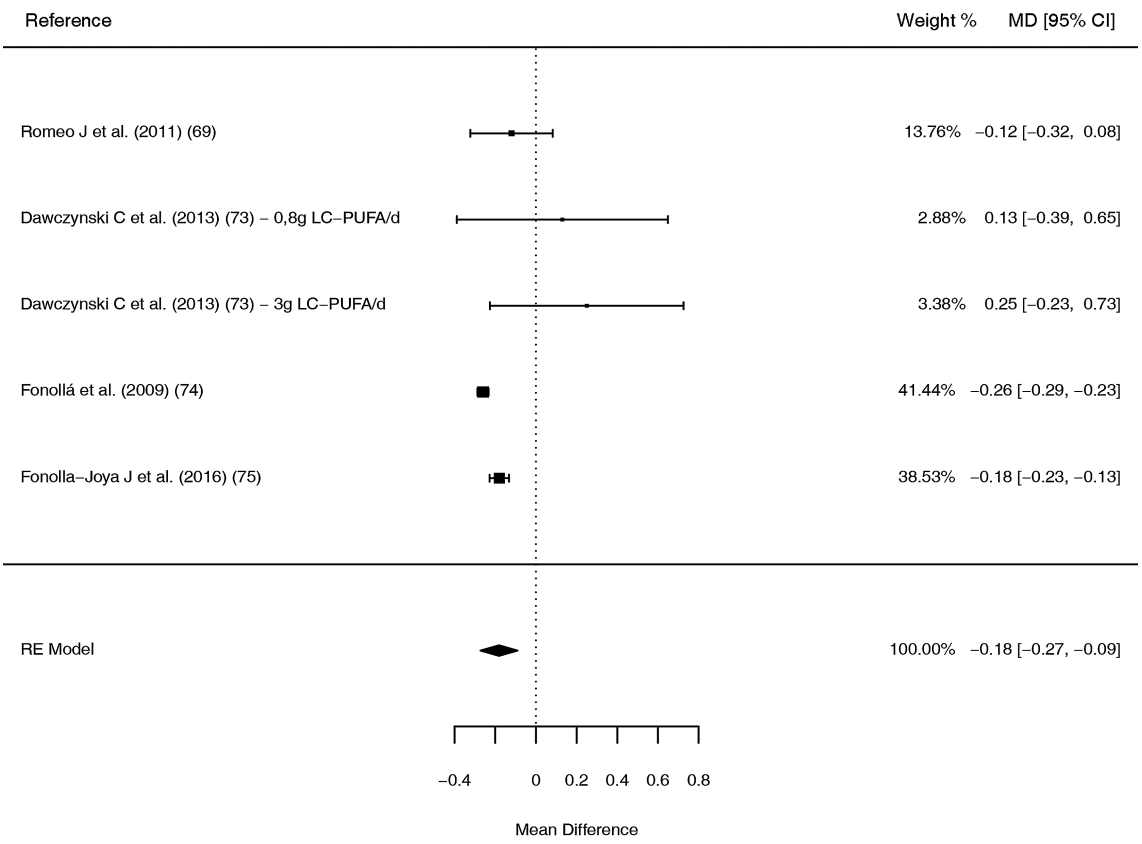

FIGURE 6 Effect size and 95% CI for fully adjusted random-effects model evaluating the influence of consumption of dairy products fortified with ω-3 FAs on LDL cholesterol plasma concentrations. Overall effect: Z = − 3.90, $P < 0.001$; Heterogeneity: $I^2 = 77.5\%$ (19.32, 99.58), Q = 15.38, df = 4, $P < 0.01$ ($n = 5$). Pooled effect estimate is represented by the black diamond. MD, mean difference; RE model, random effect model.

other spreads and their effect on LDL cholesterol; *moderate* for the meta-analyses evaluating phytosterol-fortified milk and LDL cholesterol, and phytosterol-fortified cheese and LDL cholesterol; *low* for meta-analyses evaluating yogurt and other fermented milks fortified with phytosterols and LDL cholesterol, and for ω-3 FA-fortified dairy and LDL cholesterol. Finally, it was *very low* in the case of ω-3 FA-fortified dairy and TG.

Discussion

The present systematic review was performed with the main objective of summarizing whether consumption of fortified dairy products as functional foods has any effect on biomarkers of cardiometabolic risk.

A number of systematic reviews have analyzed effects of the intake of phytosterols of diverse origins, namely, free and esterified plant sterols and stanols, when added to different foods, namely, margarines and fat spreads, mayonnaise and salad dressings, milk and dairy products, croissants and muffins, orange juice, nonfat beverages, cereal bars, and chocolate (24, 27, 29–32, 79–81).

Some meta-analyses, such as those of Ras et al. (27) and Ferguson et al. (32), have examined the effects of a variety of foods fortified with phytosterols on circulating cholesterol and LDL cholesterol plasma concentration; in particular, several intervention studies have been conducted to evaluate the action of various dairy products fortified with plant sterols/stanols on plasma lipid fractions using different study designs. Those trials confirmed the appropriateness of the dairy matrix for fortification with phytosterols intended to lower TC and LDL cholesterol in hypercholesterolemic subjects (48, 60, 63).

The present work shows that the intake of phytosterol-fortified dairy products was associated with a significant decrease in LDL cholesterol −0.36 mmol/L (95% CI: −0.41, −0.31; $P < 0.001$). However, the substantial heterogeneity among individual trials indicates that the effects of plant phytosterols on plasma LDL cholesterol concentrations are not uniform. Indeed, the study heterogeneity was mainly a result of phytosterol doses. In intervention studies with yogurt and other fermented milks, heterogeneity was not only a result of phytosterol doses, but also of BMI. According to the reviewed results, the largest reduction in LDL cholesterol was observed in subjects who consumed phytosterol-fortified cheese and butter. Furthermore, fortified regular milk and low-fat milk, as well as low-fat yogurt and yogurt drinks lead to LDL cholesterol concentration similar to those found with other foods with a fattier matrix, such as margarines and fat

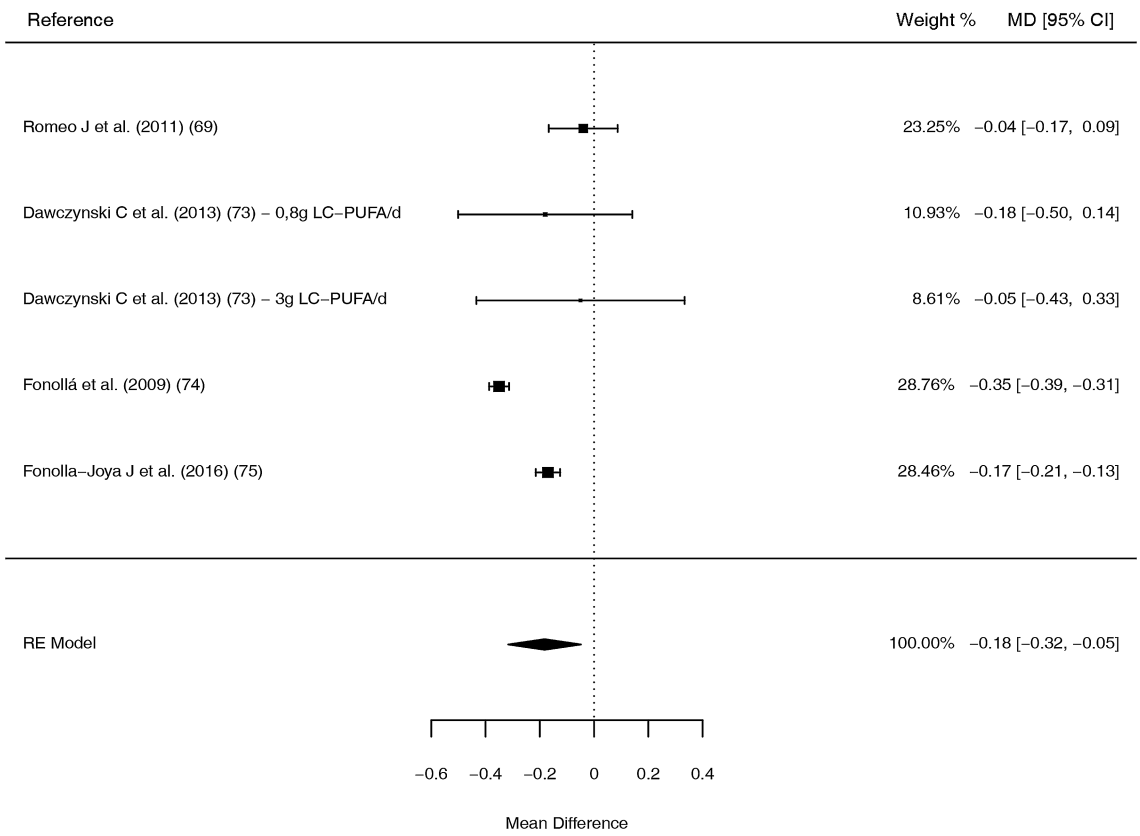

FIGURE 7 Effect size and 95% CI for fully adjusted random-effects model evaluating the influence of consumption of dairy products fortified with ω-3 FAs on TG plasma concentrations. Overall effect: Z = − 2.67, $P = 0.008$; Heterogeneity: $I^2 = 91.5\%$ (66.40, 98.82), Q = 51.40, df = 4, $P < 0.001$ ($n = 5$). Pooled effect estimate is represented by the black diamond. MD, mean difference; RE model, random effect model.

spreads (24, 27, 29–32, 79–81). This is an interesting topic for further research, as hyperlipidemic subjects are usually advised to follow a diet with a relatively low amount of fat.

Plant phytosterols reduce LDL cholesterol by interference with absorption of cholesterol present in foods, as phytosterols cause significant disruption of the cholesterol intraluminal solubilization step (82), although other mechanisms involving intestinal ATP binding cassette transporters G5 and G8 have been described (83). The relatively high efficacy of phytosterol-fortified low-fat milk and yogurt may result from incorporation of phytosterols into the milk fat globule membrane, which is enhanced by homogenization, a standard processing step in manufacture of dairy products. In fact, the external milk fat globule membrane is composed of a mixture of proteins and amphipathic lipids, including phospholipids, cholesterol, retinol, etc., and phytosterols would be located in this structure, which would facilitate fat intestinal solubilization (84). Hence, it has been suggested that phytosterols within dairy products would compete with cholesterol for transfer into the micelles, whereas in other foods, phytosterols may be trapped in the center of the lipid droplets and not be available until the fat is digested (42).

Regarding the ω-3 FA-fortification of dairy products, our results are consistent with the data of previous reviews reporting that consumption of ω-3 FA-fortified dairy products seems to modulate lipid profiles in healthy subjects and subjects with cardiovascular risk factors (35, 85). According to a review of 47 studies published by Eslick et al. (86), supplementation with ω-3 FAs improved TG concentration (−0.34 mmol/L) using fish oil as a supplementation matrix. Intake of ω-3 FAs is well known to decrease plasma TG (87), improve inflammation, and diminish the risk of coronary heart disease and stroke (88, 89). Less evidence is available about its role on blood pressure and congestive heart failure (90, 91). Moreover, according to the American Heart Association, evidence supports the consumption of seafood "1 to 2 times per week for cardiovascular benefits, including reduced risk of cardiac death, congenital heart defect, and ischemic stroke" (90). It is necessary to increase the evidence regarding the potential effects of foods commonly consumed by the general population fortified with ω-3 FAs on biomarkers of cardiometabolic risk, so that fortification can be promoted in countries with less seafood availability and consumption.

TABLE 3 Characteristics of the 2 studies analyzing the effects of the intake of dairy products fortified with vitamin D on cardiometabolic risk biomarkers in young healthy women and in women with gestational diabetes mellitus[1]

Authors (y) (ref)	Type of study (P or CO)	n (sample size)	Characteristics of the subjects: age, y; BMI, kg/m^2	Dosage, g/d	Period of intervention	TG[2], mmol/L	LDL cholesterol[2], mmol/L
Li and Xin (2016) (78)	P	97	Age: 28.6	Plain yogurt + 500 IU vitamin D3, with breakfast and dinner	16 wk	−0.26 ± −0.49	−0.4 ± −0.56
	—	C = 48	Women with gestational diabetes mellitus	—	—	—	—
	—	T = 49	—	—	—	—	—
Toxqui et al. (2013) (77)	P	165	Age: 25.6	500 mL/d dairy product fortified w/15 mg iron + 200 UI (5 μg) vitamin D3, NR	16 wk	NC	NC[3]
	—	C = 54	Young women w/low Fe stores	—	—	—	—
	—	T = 55	—	—	—	—	—

[1] DBP, diastolic blood pressure; Fe, iron; NR, pattern of consumption not reported; P, parallel; ref, reference; SBP, systolic blood pressure; TC, total cholesterol; y, year.
[2] Decrease over time expressed as mean change ± SD; NC, No changes.
[3] Changes in blood pressure: SBP -2.7 mmHg; DBP -2.6 mmHg.

Our results are consistent with previous reviews on the role of vitamin D supplementation on cardiometabolic health; in fact, the authors reported improvements in blood pressure and an independent association of low serum 25-hydroxyvitamin D (median 19 nmol/L) with all-cause and cardiovascular mortality compared with high serum 25-hydroxyvitamin D (median 70.9 nmol/L). The authors also concluded that there is scarce evidence and that well-designed studies that focus on the role of vitamin D as a modifiable risk factor are needed (92, 93).

We acknowledge a series of strengths and limitations of the present study. The major strength would be the number of studies measuring effects of dairy products fortified with phytosterols on cardiometabolic risk biomarkers that we could find and include in this systematic review (n = 31); confirming that a series of researchers have been interested in testing this topic. However, we recognize that only few studies determine the effects of fortification with ω-3 FAs (n = 8) and vitamin D (n = 2) on cardiometabolic risk biomarkers and that the blood pressure and lipid profile are not always reported as the main outcomes of these studies. Another limitation was the lack of homogeneity of the publications. The small number of subjects enrolled in the studies, the time of interventions, and the outcomes evaluated by different authors were also limitations for this systematic review. Finally, as we did not develop any screening on gray literature and limited our searches to publications in English or Spanish, there is a possibility that we did not include some trials that could have been of interest for this systematic review.

Milk and dairy products containing plant phytosterols significantly reduced LDL cholesterol plasma concentrations in moderately hyperlipidemic subjects; this decrease was mainly related to dosage. The efficacy of phytosterol-fortified dairy products was similar to that of fattier foods, suggesting the convenience of their use in lowering cholesterol in clinical treatments. Dairy products fortified with ω-3 FAs reduced LDL cholesterol and TG, these results seem to be consistent with the literature reporting that supplementation with ω-3 FAs results in an improvement of cardiometabolic risk factors. Very few studies have attempted to evaluate the effect of dairy fortification with vitamin D on cardiometabolic risk biomarkers, reflecting the need for more and well-designed research with this specific nutrient.

In conclusion, fortification of dairy products with phytosterols and ω-3 FAs seems to be a good approach to improve cardiometabolic risk biomarkers, and because of their characteristics, dairy products appear to be good vehicles to deliver these compounds to the general population. There is a need for further RCTs with similar and well-designed methodologies, greater numbers of subjects, and longer periods of time to confirm the findings of the potential effect of functional fortified dairy products on cardiometabolic health.

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